Isothiourea-Mediated One-Pot Synthesis of Trifluoromethyl Substituted 2-Pyrones

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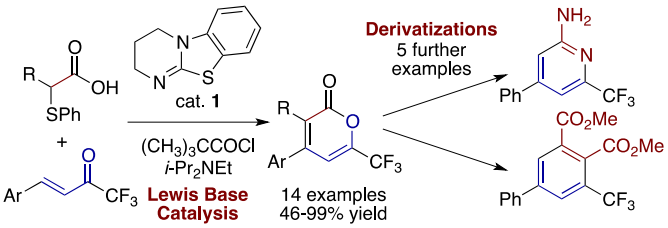
Supporting Information Placeholder

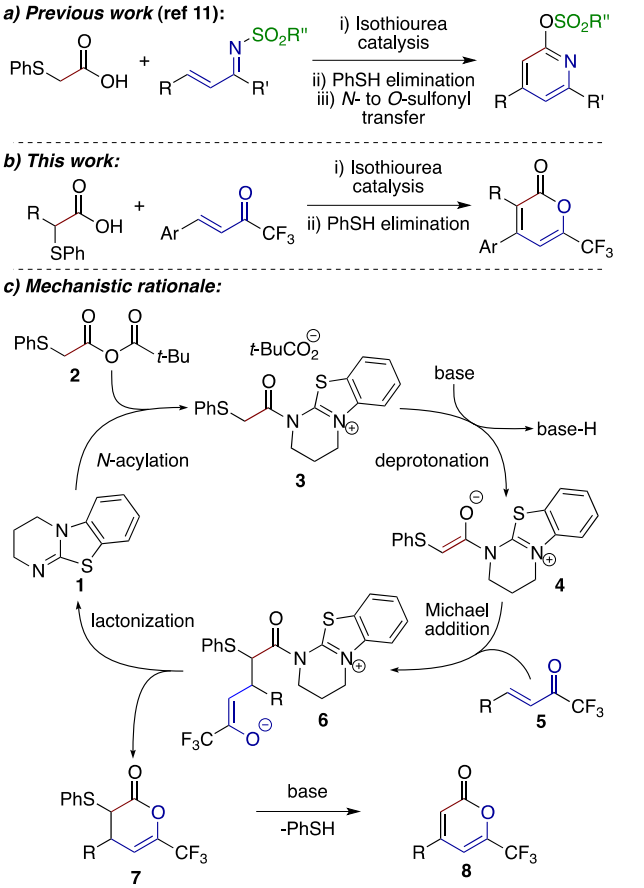


ABSTRACT: A one-pot isothiourea-mediated Michael addition/lactonization/thiol elimination cascade sequence for the formation of 4,6-disubstituted and 3,4,6-trisubstituted 2-pyrones from (phenylthio)acetic acids and α,β-unsaturated trifluoromethyl ketones is described. The synthesis of a COX-2 inhibitor and the wide-ranging derivatization of the 2-pyrone moiety to trifluoromethyl substituted aromatics and heteroaromatics is also disclosed.

2-Pyrones are a class of unsaturated heterocycle that is extremely prevelant in Nature,[1] with examples being found in plants, animals, marine organisms, bacteria, fungi and insects.[2] The parent 2-pyrone heterocycle has recently been found to have both cytotoxic and DNA-damaging effects in lung cancer cells.[3] Several examples of the 2-pyrone containing bufadienolide family of bioactive natural products have been isolated from the traditional Chinese medicine Ch'an Su, underlying their potential as theraputic agents.[4] Alongside their biological importance, 2-pyrones have also found great utility in complex molecule synthesis. Their reactivity towards both nucleophiles and electrophiles has permitted their use in the synthesis of a wide-range of high-value heterocyclic and non-heterocyclic compounds.[2,5] Despite their synthetic utility there are few routes to 2-pyrones, the most common being the tandem condensation/ cyclization of β-ketoesters,[2,6] and novel catalytic synthetic routes to these heterocycles are of significant interest.

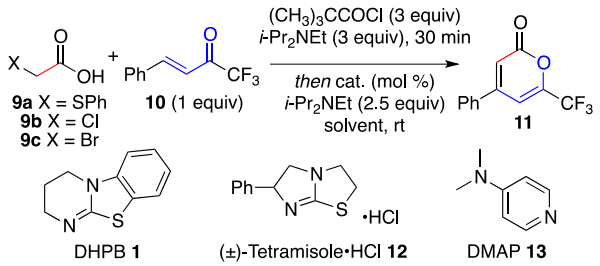
Building upon the seminal work of Romo and co-workers on the *in situ* activation of carboxylic acids[7] to generate ammonium enolates,[8] we have demonstrated that isothioureas[9] catalyze the intermolecular Michael addition/lactonization/lactamization of arylacetic acids and electron-deficient Michael acceptors.[10] This concept was further developed by incorporating a suitable leaving group within the acetic acid,[11] allowing the generation of pyridines through a cascade (Michael addition/ lactamization/elimination) sequence followed by *N*- to *O*-sulfonyl transfer (Scheme 1a). Seeking to further develop this concept, herein we report the successful development of an organocatalyzed synthesis of 2-pyrones, incorporating the pharmaceutically relevant trifluoromethyl substituent[12] at the 6-position (Scheme 1b).[13]

Scheme 1. Isothiourea-mediated One-pot Synthesis of Planar Heterocycles



Our mechanistic rationale for this transformation begins with *N*-acylation of DHPB (3,4-dihydro-2*H*-pyrimido[2,1-*b*]benzothiazole) **1** with mixed anhydride **2**, formed *in situ* from phenyl(thio)acetic acid, pivaloyl chloride and base (Scheme 1c). Deprotonation of **3** affords the (*Z*)-enolate **4**, which would undergo Michael addition to trifluoromethyl enone **5**.[14] Lactonization *via* **6** forms dihydropyrone **7** with concomitant regeneration of DHPB, and rapid off-cycle elimination of thiophenol forms the pyrone **8**.

Table 1. Reaction Optimization

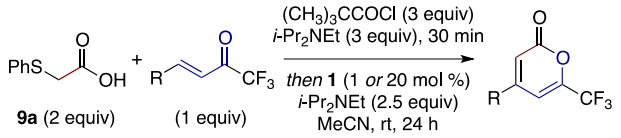


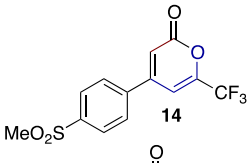
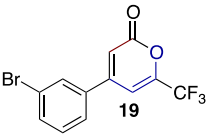
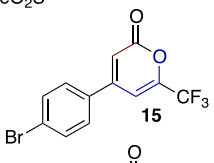
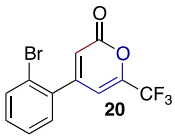
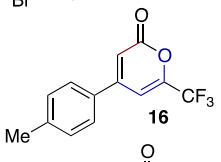
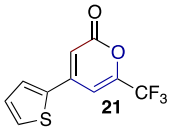
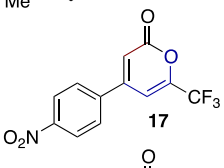
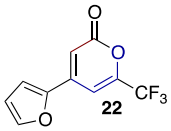
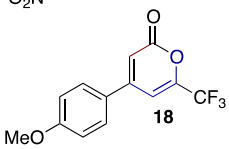
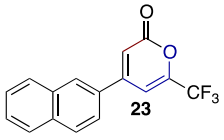
entry	acid[a]	cat. (mol %)	solvent	time (h)	yield (%)[b]
1	**9a**	**1** (20)	CH_2Cl_2	72	72
2	**9a**	**12** (20)	CH_2Cl_2	24	(52)[c]
3	**9a**	**13** (20)	CH_2Cl_2	27	(34)
4	**9a**	**1** (20)	MeCN	24	88 (99)
5	**9a**	**13** (20)	MeCN	24	50 (55)
6[d]	**9a**	**1** (20)	MeCN	24	72 (84)
7[d]	**9a**[e]	**1** (20)	MeCN	24	77
8[f]	**9a**	**1** (20)	MeCN	24	80
9[g]	**9a**	**1** (20)	MeCN	24	90
10	**9a**	**1** (1)	MeCN	24	77
11	**9a**	**1** (0.1)	MeCN	24	71
12	**9a**	-[h]	MeCN	24	59
13	**9b**	**1** (20)	MeCN	24	24
14	**9c**	**1** (20)	MeCN	24	23

[a]2 equiv of acid **9a-c**. [b]Isolated yield, NMR yield in parentheses measured against 1-methyl naphthalene as internal standard. [c]**10** not fully consumed. [d]Reaction conditions: $(CH_3)_3CCOCl$ (2 equiv), *i*-Pr_2NEt (2 equiv), *then* **1**, **10**, *i*-Pr_2NEt (2 equiv). [e]1.5 equiv **9a**. [f]Open flask conditions. [g]6 mmol **10**, 1.30 g pyrone **11** isolated. [h]Reaction in the absence of DHPB **1**.

Initially, the reaction of *in situ* activated (phenylthio)acetic acid **9a** with trifluoromethyl enone **10** in the presence of 20 mol % DHPB **1** and excess *i*-Pr_2NEt gave the desired pyrone **11** in a promising 72% isolated yield (Table 1, entry 1). Alternative Lewis bases resulted in a poor conversion into **11** according to ^1H NMR analysis of the crude reaction mixtures (entries 2 and 3). The reaction solvent was next examined, with MeCN proving superior, giving **11** in 88% isolated yield (entry 4). Attempts to reduce the equivalents of pivaloyl chloride, base, acid **9a** or performing the reaction under non-anhydrous conditions resulted in inferior yields of **11** (entries 6-8). The reaction was amenable to scale-up, affording 1.30 g of **1** in 90% yield from 6 mmol of acceptor **10** (entry 9). The catalyst loading could be reduced to 0.1 mol %, resulting in acceptable but lower isolated yields (entries 10 and 11). Surprisingly, a strong background reaction was observed, giving **11** in 59% isolated yield in the absence of isothiourea catalyst, with full consumption of **10** (entry 12). However, DHPB **1** clearly promotes the desired reaction pathway leading to higher isolated yields of **11**. Chloro- and bromoacetic acid **9b** and **9c** were also screened under these conditions, but returned low yields of **11** with full consumption of acceptor **10** (entries 13 and 14).[15]

Table 2. Reaction Scope: Variation of Trifluoromethyl Enone



product	yield[a]	product	yield[a]
 **14**	57 (95)	 **19**	73 (95)
 **15**	73 (95)	 **20**	63 (82)
 **16**	71 (88)	 **21**	45 (83)
 **17**	53 (85)	 **22**	(68)
 **18**	(61)[b]	 **23**	89 (99)

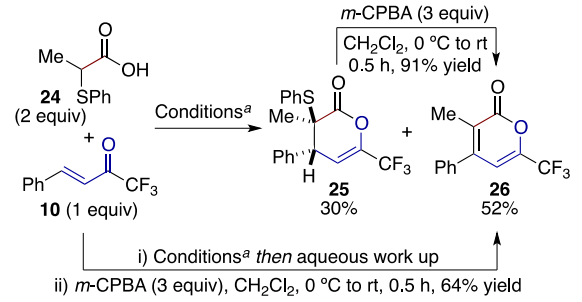
[a]Isolated yield with 1 mol % **1**, numbers in parentheses refer to isolated yield with 20 mol % **1**. [b]72 h reaction

With optimized conditions in hand, a systematic examination of the scope of the reaction with aryl substituted trifluoromethyl enones was conducted, at both 1 and 20 mol % catalyst loading (Table 2). Both electron-poor and -neutral *para*-substituted aromatics were generally well tolerated, giving high yields of pyrones **14-17** at 20 mol % loading. However, isolated yields with electron-poor aromatics were acceptable but lower at 1 mol % **1**. An extended reaction time of 72 h was required for the formation of *para*-methoxy substituted pyrone **18**, even with 20 mol % **1**. Halogen substituents at the *meta*- and *ortho*-positions (**19** and **20**) were incorporated without consequence, and heteroaromatic 2-thiophenyl and 2-furanyl substituted pyrones **21** and **22** could also be accessed in satisfactory yields. Finally, the 2-naphthalene substituted pyrone **23** was isolated in excellent yield at both 1 and 20 mol % **1**.

The possibility of introducing further substituents through the use of α-substituted (phenylthio)acetic acids to generate 3,4,6-trisubstituted pyrones was then investigated, as α,α-disubstituted acetic acids have proven to be a limiting factor in

our previous work.[10b] Whilst the reaction of α-methyl acid **24** proved sluggish at rt even using 20 mol % of **1**, heating the reaction to 95 °C in a sealed tube resulted in a separable mixture of the desired trisubstituted pyrone **26** and a single diastereoisomer of sulfide **25** that were isolated in excellent overall yield (Scheme 2). Sulfide **25** had the expected *syn* relationship between the *C*(4)H and the SPh group (as confimed by single crystal X-ray analysis), which would be unable to undergo *anti*-periplanar elimination.[16] To facilitate the desired elimination, exposure of **25** to *m*-CPBA[17] delivered pyrone **26** in 91% yield, presumably through *syn*-elimination of phenylsulfenic acid.[18] This process could be expedited, with the oxidation carried out directly on the mixture of products isolated after aqueous work-up, affording **26** in good yield. 3-Phenyl pyrone **27** could also be accessed in moderate yield.[19]

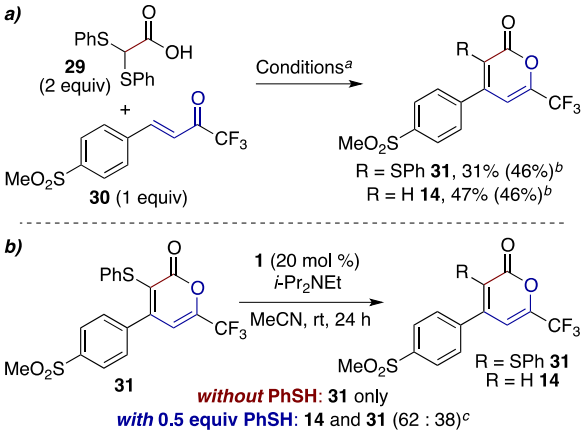
Scheme 2. 3,4,6-Trisubstituted Pyrone from α-Methyl Acid 24



[a]Reaction conditions: $(CH_3)_3CCOCl$ (3 equiv), *i*-Pr_2NEt (3 equiv), MeCN, rt, 0.5 h; *then* **1** (20 mol %), *i*-Pr_2NEt (2.5 equiv), Δ, 24 h.

To demonstrate the viability of this methodology, its application to a suitable target with established biological activity was investigated. Merck & Co. have examined trifluoromethyl substituted pyrones as COX-2 inhibitors, with 3-phenylthio substituted pyrone **31** a potent example (Scheme 3a).[20] Bis(phenylthio)acetic acid **29**[21] and acceptor **30** were considered viable precursors to this target, and their reaction generated a separable mixture of pyrones **31** and **14**.[22] To ascertain the origin of the desulfurized by-product **14**, control experiments were conducted upon isolated **31**. Resubmission of **31** to the reaction conditions (20 mol % **1**, *i*-Pr_2NEt, MeCN, rt) returned only starting material (Scheme 3b). However, when thiophenol was also added to this mixture **31** was rapidly converted into desulfurized **14**, suggesting that thiophenol eliminated during the expected reaction was causing desulfurization of **31**. Attempts to suppress this undesired reaction were unsuccessful, however **31** was accessed in 32% overall yield from commercial materials.[23]

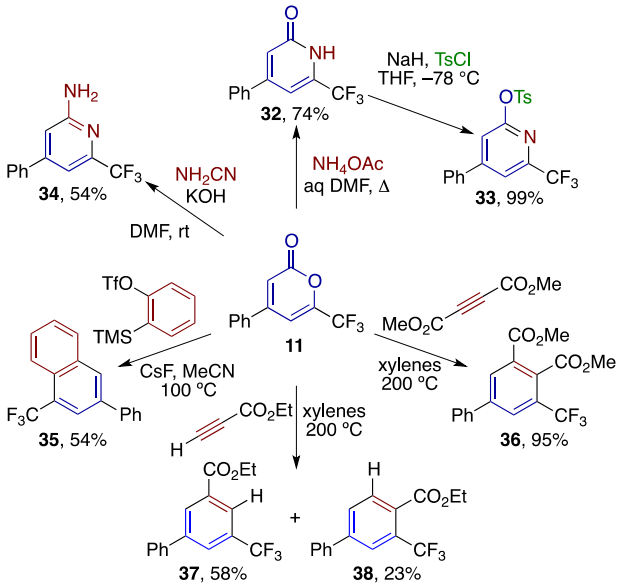
Scheme 3. Synthesis of COX-2 Inhibitor 31



[a]Reaction conditions: $(CH_3)_3CCOCl$ (3 equiv), *i*-Pr_2NEt (3 equiv), MeCN, rt, 30 mins; *then* **1** (1 *or* 20 mol %), **30**, *i*-Pr_2NEt (2.5 equiv), rt, 2 h. [b]Isolated yield with 20 mol % **1**. [c]Ratio by ^1H NMR.

Derivatization of the reactive pyrone moiety to generate further high-value products was next investigated (Scheme 4). Reaction of **11** with ammonium acetate in aqueous DMF resulted in smooth conversion into pyridone **32**. Subsequent *O*-tosylation provided 2-tosyl pyridine **33** in excellent overall yield. This provides an alternative and high yielding 3-step route to a compound synthesized in our related pyridine methodology.[11] Diels-Alder/retro-Diels-Alder sequences with benzyne and cyanamide gave the napthalene and 2-amino pyridines **34** and **35**. Furthermore, employing DMAD and ethyl propiolate generated the benzene derivatives **36-38** in excellent yield, with the latter giving a 68 : 38 (**37 : 38**) mixture of regioisomers that were readily separable by flash column chromatography.

Scheme 4. Derivatizations of Pyrone 11



In conclusion, the concise synthesis of a range of di- and trisubstituted 2-pyrones from (thiophenyl)acetic acids and readily available trifluoromethyl enones *via* an isothiourea-mediated one-pot Michael addition/ lactonization/thiol elimination sequence has been demonstrated. The efficiency of this process allows the synthesis of biologically relevant compounds with high selectivity and yield. Further investigations in our laboratory are directed towards novel applications of isothioureas in catalysis.

ASSOCIATED CONTENT

Supporting Information

General experimental procedures, characterization data, spectra, and X-ray structure of **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) (Phenylsulfinyl)-, 2-methoxy- and 2-benzyloxyacetic acid were also tested, but all gave intractable mixtures of products.

(16) See the Supporting Information. CCDC 974564 (**25**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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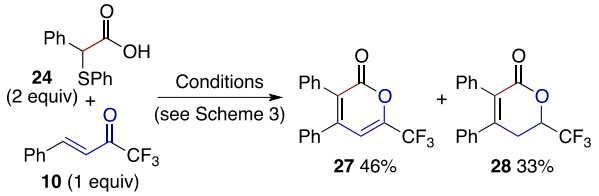
(18) Resubmission of isolated sulfide **25** to the reaction conditions (DHPB **1**, *i*-Pr_2NEt, MeCN, Δ) returned only starting material.

(19) 3-Phenyl substituted pyrone **27** was isolated along with the dihydropyrone **28**, presumably resulting from thiophenol-mediated desulfurization of the phenyl analogue of sulfide **25**, and tautomerisation. See the Supporting Information for details.



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(22) Ratios of **31** to **14** by crude ^{1}H NMR were 45:55 and 50:50 at 1 and 20 mol % respectively.

(23) See the Supporting Information for details.

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